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Research Report

Pharmacological characterization of (S)-(2)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine HCl (SIB-1508Y, Altinicline), a novel nicotinic acetylcholine receptor agonist

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ABSTRACT

(S)-(2)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine HCl (SIB-1508Y, Altinicline), is a subtype-selective neuronal nicotinic acetylcholine receptor (nAChR) agonist. In rodents, SIB-1508Y exhibited antidepressant activity, reversed age-related decrements in vigilance, and improved motor and cognitive function in primate models of Parkinson's disease. The goal of the study was to explore neurochemical effects of SIB-1508Y and its isomer, SIB-1680WD. *In vitro*, SIB-1508Y increased dopamine (DA) release from slices of rat striatum, nucleus accumbens (NAc), olfactory tubercles (OT) and prefrontal cortices (PFC) in a concentration-dependent manner. Relative to its robust effects on DA release from various brain regions, SIB-1508Y was minimally effective at increasing NE release from hippocampus or PFC, and 5-HT release from PFC. SIB-1680WD was less potent and efficacious than SIB-1508Y, but did not act as a partial agonist. Subcutaneous injection of SIB-1508Y (10 mg/kg) increased striatal DA release and this release was sensitive to blockade by the non-competitive nAChR antagonist, mecamylamine (Mec). SIB-1508Y also increased hippocampal ACh release selectively without affecting striatal ACh release. Hippocampal ACh release evoked by SIB-1508Y was attenuated by nAChR antagonists Mec and Dihydro-β-erythroidine (DHβE), and also by the DA D1 receptor antagonist, SCH-23390. These results are consistent with previously established pharmacology of nAChR regulation of hippocampal ACh release. Repeated administration of SIB-1508Y did not result in an enhanced striatal DA release or hippocampal ACh release. In summary, the abilities of SIB-1508Y to release multiple neurotransmitters in distinct brain regions may contribute to its behavioral profile.

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1. Introduction

Neuronal nicotinic receptors (nAChRs) are members of the ligand-gated ion channel family. The gene family is comprised of nine α-subunits (α2–α10) and three β-subunits (β2–β4). The composition of native receptors in the brain is largely unknown and it is believed that heteromeric receptors containing be α4 and β2 subunits and the homomeric α7 receptor constitute the majority, although other combinations certainly exist (Role and Berg, 1996; Arneric and Brioni, 1999; Dani and Bertrand, 2007; Gotti et al., 2007; McKay et al., 2007).

The nAChRs have multiple physiological functions and it has been proposed that subtype-selective nAChR ligands will have clinical utility in the treatment of pain, smoking cessation, Alzheimer's disease and Parkinson's disease (Arneric and Brioni, 1999; Bontempi et al., 2001; Menzaghi et al., 1999; Lloyd et al., 1998; Rollema et al., 2007; Picciotto and Zoli, 2008). Our search for novel subtype-selective ligands led to the discovery of (S)-(2)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (SIB-1508Y in its HCl salt form), an α4β2 selective nAChR ligand (Cosford et al., 1996, 2003), the active isomer of (±)-(2)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine (fumarate salt form; SIB-1765F; Sacaan et al., 1997; Menzaghi et al., 1999). SIB-1508Y exhibited activity in rodent models of depression (Ferguson et al., 2000), improved cognitive function in monkeys treated with low dose of MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) and motor function in Parkinsonian monkeys that received higher doses of MPTP (Schneider et al., 1999, 1998). SIB-1508Y and its racemic form (SIB-1765F) were shown to improve speed and accuracy of performance in poorly performing rats (Grottick and Higgins, 2000; Grottick et al., 2000a,b) and to reverse age-related decrements in vigilance in rats (Grottick et al., 2003). The neurochemical profile of SIB-1508Y that underlies these diverse pharmacological effects has not been examined in detail. The present investigation describes *in vitro* and *in vivo* neuropharmacological characterization of SIB-1508Y.

2. Results

The racemic compound, SIB-1765 and its two isomers, SIB-1508Y and SIB-1680WD displaced the binding of [^{3}H]-Nic to rat brain cortical membranes in a concentration-dependent manner. SIB-1765F and SIB-1508Y were equipotent (IC_{50} values of 3–5 nM) and both ligands were 15-fold more potent than the less active isomer, 1680WD (IC_{50} value of 75 nM). All three ligands displaced [^{3}H]-QNB binding with micromolar potency (IC_{50} values in the range of 4.5–10 μM; Fig. 1). SIB-1508Y was extensively evaluated in a panel of ligand binding and enzymatic assays at Pan Labs covering a wide range of ligand-gated ion channels, G-protein coupled receptors, enzymes involved in neurotransmitter biosynthesis and degradation. SIB-1508Y did not show appreciable affinity to any of these targets at concentrations as high as 10 μM (data not shown).

2.1. *In vitro neurotransmitter release*

SIB-1765F and its two isomers, SIB-1508Y and SIB-1680WD were examined for their effects on the striatal DA release and hippocampal NE release in slice superfusion assays. In striatal DA release assay, SIB-1508Y was more potent than

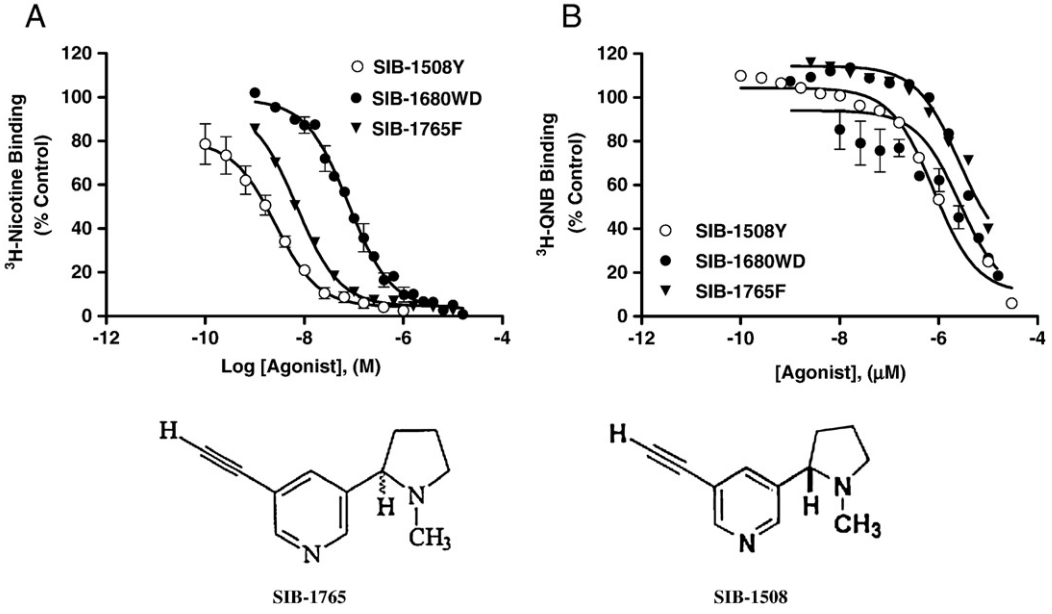

Fig. 1 – Concentration-related effects of SIB-1765F, SIB-1508Y and SIB-1680WD on the binding of [^{3}H]-NIC (A) and [^{3}H]-QNB to rat cortical membranes (B). Data represent mean ± SEM (n = 3–5 experiments each with 2–3 replicates). The IC_{50} values for inhibition of [^{3}H]-NIC binding for SIB-1765F, SIB-1508Y and SIB-1680WD are 4.6, 3.0 and 75 nM, respectively. The corresponding values for inhibition of [^{3}H]-QNB binding for SIB-1765F, SIB-1508Y and SIB-1680WD are 10,000, 8900 and 4500 nM, respectively. Structures of SIB-1765 (racemic mixture) and SIB-1508 ((S)-enantiomer) are shown.